(FILE 'HOME' ENTERED AT 14:41:34 ON 26 FEB 2002)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, BIOSIS, MEDICONF'
ENTERED AT 14:52:52 ON 26 FEB 2002

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L1          21 S DAF-18 AND PTEN
L2        3582 S DAF-18 OR DAF18 OR PTEN
L3          21 S L1 AND (ELEGANS OR MAMMAL)
L4           5 DUP REM L3 (16 DUPLICATES REMOVED)
L5           5 SORT L4 PY
L6         200 S L2 AND PY<=1997
L7         100 DUP REM L6 (100 DUPLICATES REMOVED)
L8          53 S L7 AND (MODULATE? OR INCREASE? OR DECREASE? OR ENHANCE? OR S
L9          53 SORT L8 PY
L10          3 S L9 NOT PTEN

=> d an ti so au ab pi l5 1-5

L5   ANSWER 1 OF 5     MEDLINE
AN   1999102962     MEDLINE
TI   The C. elegans PTEN homolog, DAF-18
     , acts in the insulin receptor-like metabolic signaling pathway.
SO   MOLECULAR CELL, (1998 Dec) 2 (6) 887-93.
     Journal code: C5E; 9802571. ISSN: 1097-2765.
AU   Ogg S; Ruvkun G
AB   An insulin-like signaling pathway, from the DAF-2 receptor, the AGE-1
     phosphoinositide 3-kinase, and the AKT-1/AKT-2 serine/threonine kinases to
     the DAF-16 Fork head transcription factor, regulates the metabolism,
     development, and life span of Caenorhabditis elegans. Inhibition
     of daf-18 gene activity bypasses the normal
     requirement for AGE-1 and partially bypasses the need for DAF-2 signaling.
     The suppression of age-1 mutations by a daf-18
     mutation depends on AKT-1/AKT-2 signaling, showing that DAF-
     18 acts between AGE-1 and the AKT input to DAF-16 transcriptional
     regulation. daf-18 encodes a homolog of the human
     tumor suppressor PTEN (MMAC1/TEP1), which has 3-phosphatase
     activity toward phosphatidylinositol 3,4,5-trisphosphate (PIP3).
     DAF-18 PTEN may normally limit AKT-1 and AKT-2
     activation by decreasing PIP3 levels. The action of daf-
     18 in this metabolic control pathway suggests that mammalian
     PTEN may modulate insulin signaling and may be variant in diabetic
     pedigrees.

L5   ANSWER 2 OF 5     MEDLINE
AN   1999307426     MEDLINE
TI   The PTEN tumor suppressor homolog in Caenorhabditis
     elegans regulates longevity and dauer formation in an insulin
     receptor-like signaling pathway.
SO   PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF
     AMERICA, (1999 Jun 22) 96 (13) 7427-32.
     Journal code: PV3; 7505876. ISSN: 0027-8424.
AU   Mihaylova V T; Borland C Z; Manjarrez L; Stern M J; Sun H
AB   Inactivation of the tumor suppressor PTEN gene is found in a
     variety of human cancers and in cancer predisposition syndromes. Recently,
     PTEN protein has been shown to possess phosphatase activity on
     phosphatidylinositol 3,4,5-trisphosphate, a product of
     phosphatidylinositol 3-kinase. We have identified a homolog of
     PTEN in Caenorhabditis elegans and have found that it
     corresponds to the daf-18 gene, which had been defined
     by a single, phenotypically weak allele, daf-18
     (e1375). By analyzing an allele, daf-18(nr2037), which
     bears a deletion of the catalytic portion of CePTEN/DAF-
     18, we have shown that mutation in daf-18 can
     completely suppress the dauer-constitutive phenotype caused by
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inactivation of daf-2 or age-1, which encode an insulin receptor-like molecule and the catalytic subunit of phosphatidylinositol 3-kinase, respectively. In addition, **daf-18**(nr2037) dramatically shortens lifespan, both in a wild-type background and in a daf-2 mutant background that normally prolongs lifespan. The lifespan in a **daf-18**(nr2037) mutant can be restored to essentially that of wild type when combined with a daf-2 mutation. Our studies provide genetic evidence that, in C. **elegans**, the **PTEN** homolog **DAF-18** functions as a negative regulator of the DAF-2 and AGE-1 signaling pathway, consistent with the notion that **DAF-18** acts a phosphatidylinositol 3,4,5-trisphosphate phosphatase in vivo. Furthermore, our studies have uncovered a longevity-promoting activity of the **PTEN** homolog in C. **elegans**.

L5 ANSWER 3 OF 5 MEDLINE
AN 1999227332 MEDLINE
TI Regulation of dauer larva development in Caenorhabditis **elegans** by **daf-18**, a homologue of the tumour suppressor **PTEN**.
SO CURRENT BIOLOGY, (1999 Mar 25) 9 (6) 329-32.
Journal code: B44; 9107782. ISSN: 0960-9822.
AU Rouault J P; Kuwabara P E; Sinilnikova O M; Duret L; Thierry-Mieg D; Billaud M
AB The tumour suppressor gene **PTEN** (also called MMAC1 or TEP1) is somatically mutated in a variety of cancer types [1] [2] [3] [4]. In addition, germline mutation of **PTEN** is responsible for two dominantly inherited, related cancer syndromes called Cowden disease and Bannayan-Ruvalcaba-Riley syndrome [4]. **PTEN** encodes a dual-specificity phosphatase that inhibits cell spreading and migration partly by inhibiting integrin-mediated signalling [5] [6] [7]. Furthermore, **PTEN** regulates the levels of phosphatidylinositol 3,4,5-trisphosphate (PIP3) by specifically dephosphorylating position 3 on the inositol ring [8]. We report here that the dauer formation gene **daf-18** is the Caenorhabditis **elegans** homologue of **PTEN**. **DAF-18** is a component of the insulin-like signalling pathway controlling entry into diapause and adult longevity that is regulated by the DAF-2 receptor tyrosine kinase and the AGE-1 PI 3-kinase [9]. Others have shown that mutation of **daf-18** suppresses the life extension and constitutive dauer formation associated with daf-2 or age-1 mutants. Similarly, we show that inactivation of **daf-18** by RNA-mediated interference mimics this suppression, and that a wild-type **daf-18** transgene rescues the dauer defect. These results indicate that **PTEN**/**daf-18** antagonizes the DAF-2-AGE-1 pathway, perhaps by catalyzing dephosphorylation of the PIP3 generated by AGE-1. These data further support the notion that mutations of **PTEN** contribute to the development of human neoplasia through an aberrant activation of the PI 3-kinase signalling cascade.

L5 ANSWER 4 OF 5 MEDLINE
AN 1999178991 MEDLINE
TI Regulation of the insulin-like developmental pathway of Caenorhabditis **elegans** by a homolog of the **PTEN** tumor suppressor gene.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Mar 16) 96 (6) 2925-30.
Journal code: PV3; 7505876. ISSN: 0027-8424.
AU Gil E B; Malone Link E; Liu L X; Johnson C D; Lees J A
AB The human **PTEN** tumor suppressor gene is mutated in a wide variety of sporadic tumors. To determine the function of **PTEN** in vivo we have studied a **PTEN** homolog in Caenorhabditis **elegans**. We have generated a strong loss-of-function allele of the **PTEN** homolog and shown that the deficient strain is unable to enter dauer diapause. An insulin-like phosphatidylinositol 3-OH kinase (PI3'K) signaling pathway regulates dauer-stage entry. Mutations in either

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the daf-2 insulin receptor-like (IRL) gene or the age-1 encoded PI3'K catalytic subunit homolog cause constitutive dauer formation and also affect the life span, brood size, and metabolism of nondauer animals. Strikingly, loss-of-function mutations in the age-1 PI3'K and daf-2 IRL genes are suppressed by loss-of-function mutations in the **PTEN** homolog. We establish that the **PTEN** homolog is encoded by **daf-18**, a previously uncloned gene that has been shown to interact genetically with the DAF-2 IRL AGE-1 PI3'K signaling pathway. This interaction provides clear genetic evidence that **PTEN** acts to antagonize PI3'K function in vivo. Given the conservation of the PI3'K signaling pathway between C. **elegans** and **mammals**, the analysis of **daf-18 PTEN** mutant nematodes should shed light on the role of human **PTEN** in the etiology of metabolic disease, aging, and cancer.

L5 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2002 ACS
AN 2000:384548 CAPLUS
DN 133:39116
TI Genes and polypeptides involved in insulin signaling pathways for glucose tolerance, obesity, and longevity and their uses as therapeutic and diagnostic tools
SO PCT Int. Appl., 402 pp.
CODEN: PIXXD2
IN Ruvkun, Gary; Ogg, Scott
AB Disclosed herein are novel genes and methods for the screening of therapeutics useful for treating impaired glucose tolerance conditions, as well as diagnostics and therapeutic compns. for identifying or treating such conditions. The Caenorhabditis **elegans** metabolic regulatory genes daf-2 and age-1 encode homologs of the mammalian insulin receptor/phosphoinositol 3-kinase signaling pathway proteins, resp. Also, the C. **elegans** PKB kinase and AKT kinase act downstream of these genes, as their mammalian homologs act downstream of insulin signaling. The C. **elegans PTEN** lipid phosphatase homolog, **DAF-18**, acts upstream of AKT in this signaling pathway. Further, the DAF-16 forkhead protein represents the major transcriptional output of this insulin signaling pathway. Addnl. evidence indicates that the DAF-16, DAF-3, DAF-8, and DAF-14 transcriptional outputs of converging signaling pathways regulate metab. The congruence between the C. **elegans** and mammalian insulin signaling pathways strongly supports the contention that new genes identified in the C. **elegans** pathway also act in mammalian insulin signaling. Exemplary sequences and functional characteristics of the C. **elegans** daf genes and their human homologs are provided.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000033068	A1	20000608	WO 1999-US28529	19991202
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2001029617	A1	20011011	US 1998-205658	19981203
	EP 1163515	A1	20011219	EP 1999-960641	19991202
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

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L4           5 DUP REM L3 (16 DUPLICATES REMOVED)
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L6         200 S L2 AND PY<=1997
L7         100 DUP REM L6 (100 DUPLICATES REMOVED)
L8          53 S L7 AND (MODULATE? OR INCREASE? OR DECREASE? OR ENHANCE? OR S
L9          53 SORT L8 PY
L10          3 S L9 NOT PTEN

=> d an ti so au ab l10 1-3

L10  ANSWER 1 OF 3     MEDLINE
AN   96170778     MEDLINE
TI   The age-1 and daf-2 genes function in a common pathway to control the
     lifespan of Caenorhabditis elegans.
SO   GENETICS, (1995 Dec) 141 (4) 1399-406.
     Journal code: FNH; 0374636. ISSN: 0016-6731.
AU   Dorman J B; Albinder B; Shroyer T; Kenyon C
AB   Recessive mutations in two genes, daf-2 and age-1, extend the lifespan of
     Caenorhabditis elegans significantly. The daf-2 gene also regulates
     formation of an alternative developmental state called the dauer. Here we
     asked whether these two genes function in the same or different lifespan
     pathways. We found that the longevity of both age-1 and daf-2 mutants
     requires the activities of the same two genes, daf-16 and daf-
     18. In addition, the daf-2(e1370); age-1(hx546) double mutant did
     not live significantly longer than the daf-2 single mutant. We also found
     that, like daf-2 mutations, the age-1(hx546) mutation affects certain
     aspects of dauer formation. These findings suggest that age-1 and daf-2
     mutations do act in the same lifespan pathway and extend lifespan by
     triggering similar if not identical processes.

L10  ANSWER 2 OF 3     MEDLINE
AN   95309673     MEDLINE
TI   Genes that regulate both development and longevity in Caenorhabditis
     elegans.
SO   GENETICS, (1995 Apr) 139 (4) 1567-83.
     Journal code: FNH; 0374636. ISSN: 0016-6731.
AU   Larsen P L; Albert P S; Riddle D L
AB   The nematode Caenorhabditis elegans responds to conditions of overcrowding
     and limited food by arresting development as a dauer larva. Genetic
     analysis of mutations that alter dauer larva formation (daf mutations) is
     presented along with an updated genetic pathway for dauer vs. nondauer
     development. Mutations in the daf-2 and daf-23 genes double adult life
     span, whereas mutations in four other dauer-constitutive genes positioned
     in a separate branch of this pathway (daf-1, daf-4, daf-7 and daf-8) do
     not. The increased life spans are suppressed
     completely by a daf-16 mutation and partially in a daf-2; daf-
     18 double mutant. A genetic pathway for determination of adult
     life span is presented based on the same strains and growth conditions
     used to characterize Daf phenotypes. Both dauer larva formation and adult
     life span are affected in daf-2; daf-12 double mutants in an
     allele-specific manner. Mutations in daf-12 do not extend adult life span,
     but certain combinations of daf-2 and daf-12 mutant alleles nearly
     quadruple it. This synergistic effect, which does not equivalently extend
     the fertile period, is the largest genetic extension of life span yet
     observed in a metazoan.

L10  ANSWER 3 OF 3     MEDLINE
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AN 92120509 MEDLINE
TI Genetic analysis of chemosensory control of dauer formation in Caenorhabditis elegans.
SO GENETICS, **(1992 Jan)** 130 (1) 105-23.
Journal code: FNH; 0374636. ISSN: 0016-6731.
AU Vowels J J; Thomas J H
AB Dauer larva formation in Caenorhabditis elegans is controlled by chemosensory cells that respond to environmental cues. Genetic interactions among mutations in 23 genes that affect dauer larva formation were investigated. Mutations in seven genes that cause constitutive dauer formation, and mutations in 16 genes that either block dauer formation or result in the formation of abnormal dauers, were analyzed. Double mutants between dauer-constitutive and dauer-defective mutations were constructed and characterized for their capacity to form dauer larvae. Many of the genes could be interpreted to lie in a simple linear epistasis pathway. Three genes, daf-16, **daf-18** and daf-20, may affect downstream steps in a branched part of the pathway. Three other genes, daf-2, daf-3 and daf-5, displayed partial or complex epistasis interactions that were difficult to interpret as part of a simple linear pathway. Dauer-defective mutations in nine genes cause structurally defective chemosensory cilia, thereby blocking chemosensation. Mutations in all nine of these genes appear to fall at a single step in the epistasis pathway. Dauer-constitutive mutations in one gene, daf-11, were strongly **suppressed** for dauer formation by mutations in the nine cilium-structure genes. Mutations in the other six dauer-constitutive genes caused dauer formation despite the absence of functional chemosensory endings. These results suggest that daf-11 is directly involved in chemosensory transduction essential for dauer formation, while the other Daf-c genes play roles downstream of the chemosensory step.

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L9          53 SORT L8 PY
L10          3 S L9 NOT PTEN
L11         43 S DAF-18 OR DAF18
L12         12 DUP REM L11 (31 DUPLICATES REMOVED)
L13         12 SORT L12 1-12 PY
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13	4	DAF-$5 and DAF-18	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/02/26 14:31
19	39	glucose AND diabet$5 AND obes$10 AND elegans	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/02/26 14:32
25	5	(glucose AND diabet$5 AND obes$10 AND elegans) and DAF-$5	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/02/26 14:35
31	4	DAF-$5 and PTEN	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/02/26 14:35